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(12) **Patent Application:** (11) **CA 2015114**

(54) 4-/4'-HALOPHENYL/-2-METHYL-1,2,3,4-TETRAHYDROISOQUINOLINES AND A METHOD FOR THEIR PREPARATION

(54) 4-(4'-HALOPHENYL)-2-METHYL-1,2,3,4-TETRAHYDRO-ISOQUINOLINES ET METHODE DE PREPARATION

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ABSTRACT:

ABSTRACT OF THE DISCLOSURE: 4-/4'-halophenyl/2-methyl-1,2,3,4-tetrahydroisoquinoline racemate or optically active isomer having the formula: Image wherein R is a member selected from brome or fluor, and their physiologically acceptable salts. These have high inhibitory effect towards dopamine noradrenaline or serotonin uptake, as well as high antiulcer activity. A method for the preparation, is characterised in that benzylmethylamine is alkylated with at least one .alpha.halogenated aryl aliphatic ketone to 2-/N-methyl-N-benzylamin/-4-haloacetophenone, and then reduced to Nbenzyl-2-methylamine-1-/4-halophenyl/-1-ethanol with sodium borhydrate. The latter is cyclodehydrated with concentrated sulphuric acid.

CLAIMS: Show all claims

*** Note: Data on abstracts and claims is shown in the official language in which it was submitted.

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Patent Document Number 2015114 :

4-/4'-HALOPHENYL/-2-METHYL-1,2,3,4-TETRAHYDROISOQUINOLINES AND A METHOD FOR THEIR PREPARATION

4-(4'-HALOPHENYL)-2-METHYL-1,2,3,4-TETRAHYDRO-ISOQUINOLINES ET METHODE DE PREPARATION

CLAIMS:

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. At least one 4-/4'-halophenyl/-2-methyl-

1,2,3,4,-tetrahydroisoquinoline racemate or optically active isomer having the formula:
Image wherein R is a member selected from brome or fluor, and their physiologically acceptable salts.

2. The product of claim 1, wherein R is brome.

3. The product of claim 1, wherein R is fluor.

4. The product of claim 1, being a racemate.

5. The product of claim 1, being an optically active isomer.

6. The product of claim 1, being a physiological active salt.

7. A method for the preparation, of at least one racemic tetrahydroisoquinoline as defined in claim 1, characterized that benzylmethylamine is alkylated with at

least one .alpha.-halogenated aryl aliphatic ketone to 2-/N- methyl-N-benzylamin/-4-haloacetophenone, and then reduced to N-benzyl-2-methylamine-1-/4-halophenyl/-1-ethanol with sodium borhydrate, and the latter is cyclodehydrated with concentrated sulphuric acid.

8. A Method for the preparation of optically active tetrahydroisoquinolones as defined in claim 1, characterized that a racemic tetrahydroisoquinolone is treated with at least one optically active acid.

9. The method as defined in 7, characterized that the alkylating of said benzylmethylamine is carried out in acetone or benzol medium at twice molar excess of the latter per mole of the ketone.

10. The method as defined claim 7, characterized that said reduction of said acetophenone is carried out in a medium of lower alcohols at a temperature interval from 10 to 80°C.

11. The method as defined in claim 7, characterized in that the cyclization of said ethanol is carried out in dichloromethane or dichloroethane medium at a temperature ranging from 0 to 30°C.

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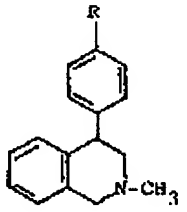
The invention concerns 4-/4'-halophenyl/-2-methyl-1,2,3,4,-tetrahydroisoquinolines racemates or optically active antipodes and a method for their preparation.

It is known from K. Kunetmen, H. Gerhards, H. Kruse, M. Leven, E. Paulus, U. Schacht, K. Schmitt, J. Med. Chem. 1987, 30, 7988-804 that racemic or optically active 4-phenyl-8-amino-2-methyl-1,2,3,4,-tetrahydroisoquinolines, possess inhibitory effect on the uptake of dopamine/DA/, noradrenaline/NA/ and serotonin/5-HT/ from synaptosomes of rats' cerebral cortex.

It is also known from M. Bickel, Arzneim-Forsch: Drug Res., 30(1), No 1, 69, 1980, that the racemic 4-phenyl-8-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline possesses moderate inhibitory effect towards stress inducing stomach ulcers in rats.

The object of the invention is to create new 4-/4'-halophenyl/-2-methyl-1,2,3,4,-tetrahydroisoquinolines having general formula (I):



Ia R = Br
Ib R = F

where R means brome or fluor, and their physiologically acceptable salts, which have high inhibitory effect towards dopamine, noradrenaline or serotonin uptake, as well as a high antiulcer activity.

The essence of the invention comprises in the fact that the racemic compounds with general formula I are obtained according to the following three-stage reaction scheme:

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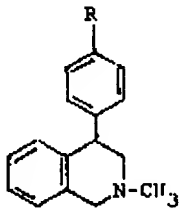
ABSTRACT OF THE DISCLOSURE:

4-/4'-halophenyl/2-methyl-1,2,3,4-tetrahydroisoquinoline racemate or optically active isomer having the formula:



wherein R is a member selected from bromo or fluor, and their physiologically acceptable salts. These have high inhibitory effect towards dopamine noradrenaline or serotonin uptake, as well as high antiulcer activity. A method for the preparation, is characterised in that benzylmethylamine is alkylated with at least one α-halogenated aryl aliphatic ketone to 2-/N-methyl-N-benzylamin/-4-haloacetophenone, and then reduced to N-benzyl-2-methylamine-1-/4-halophenyl/-1-ethanol with sodium borhydrate. The latter is cyclodehydrated with concentrated sulphuric acid.